

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Application of: Irun R. COHEN et al.

Confirmation No.: 5950

Patent No.: 7,118,744 B2

Application No.: 10/032,482

Patent Date: October 10, 2006

Filing Date: January 2, 2002

For: IMMUNOGENIC COMPOSITIONS FOR  
INDUCTION OF ANTI-TUMOR  
IMMUNITY

Attorney Docket No.: 85189-700

**REQUEST FOR CERTIFICATE OF CORRECTION UNDER 37 C.F.R. § 1.322**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

Patentees hereby respectfully request the issuance of a Certificate of Correction in connection with the above-identified patent. The corrections are listed on the attached Form PTO-1050. The corrections requested are as follows:

**Title Page:**

Item (56) **References Cited**, OTHER PUBLICATIONS, Lee et al. reference, after “DNA damage in the form of insertion/” delete “deletin” and insert -- deletion --. Support for this change appears on applicants’ PTO/SB08A filed January 2, 2002.

**Column 29:**

Line 61 (claim 1, line 2), after “p53, which peptide is 7 to 30 amino” delete “acids” and insert -- acid residues --.

Line 63 (claim 1, line 4), after “of a CDR of the heavy” delete “chain”.

Support for the above changes appear in application claim 8.

**Column 31:**

Line 27 (claim 7, line 8), after “Asn-Tyr-Asn-Gln-” insert -- Asn- --.

Line 57 (claim 7, line 20), after “Ser-” delete “Phr” and insert -- Phe --.

Line 61 (claim 7, line 23), after “(421 VH), and peptide IVc containing the” delete “DCR3” and insert --CDR3 --.

Support for the above changes appear in application claim 19.

Column 32:

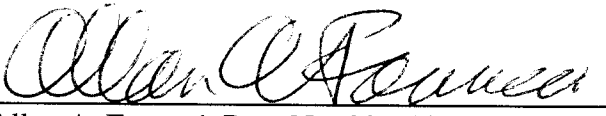
Line 48 (claim 11, line 30), after "(IVc) Trp-Gln-Gly-Thr-His-Ser-Pro-Leu-Thr (SEQ ID NO:20)" delete "." and insert -- ; --. Support for this change appears in application claim 24

The requested corrections are for errors that appear to have been made by the Office. Therefore, no fee is believed to be due for this request. Should any fees be required, however, please charge such fees to Winston & Strawn LLP Deposit Account No. 50-1814. Please issue a Certificate of Correction in due course.

Respectfully submitted,

Date

10/31/06



Allan A. Fanucci, Reg. No. 30,256

**WINSTON & STRAWN LLP**  
**Customer No. 28765**

212-294-3311

**UNITED STATES PATENT AND TRADEMARK OFFICE  
CERTIFICATE OF CORRECTION**

PATENT NO.: 7,118,744 B2

Page 1 of 1

APPLICATION NO.: 10/032,482

DATED: Oct. 10, 2006

INVENTOR(S): Cohen et al.

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title Page:

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Column 29:

Line 61, after "p53, which peptide is 7 to 30 amino" delete "acids" and insert -- acid residues --.

Line 63, after "of a CDR of the heavy" delete "chain".

Column 31:

Line 27, after "Asn-Tyr-Asn-Gln-" insert -- Asn- --.

Line 57, after "Ser-" delete "Phr" and insert -- Phe --.

Line 61, after "(421 VH), and peptide IVc containing the" delete "DCR3" and insert --CDR3 --.

Column 32:

Line 48, after "(IVc) Trp-Gln-Gly-Thr-His-Ser-Pro-Leu-Thr (SEQ ID NO:20)" delete "." and insert -- ; --.



US007118744B2

(12) **United States Patent**  
**Cohen et al.**(10) **Patent No.:** **US 7,118,744 B2**  
(45) **Date of Patent:** **Oct. 10, 2006**(54) **IMMUNOGENIC COMPOSITIONS FOR  
INDUCTION OF ANTI-TUMOR IMMUNITY**(75) Inventors: **Irun R Cohen**, Rehovot (IL); **Varda Rotter**, Rishon LeZion (IL); **Roland Wolkowicz**, Redwood City, CA (US); **Pedro Ruiz**, Stanford, CA (US); **Neta Erez-Alon**, Tel Aviv (IL); **Johannes Herkel**, Wuerzburg (DE)(73) Assignee: **Yeda Research and Development Co., Ltd.**, Rehovot (IL)

(\*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 259 days.

(21) Appl. No.: **10/032,482**(22) Filed: **Jan. 2, 2002**(65) **Prior Publication Data**

US 2002/0197270 A1 Dec. 26, 2002

**Related U.S. Application Data**

(62) Division of application No. 09/445,602, filed as application No. PCT/IL98/00266 on Jun. 9, 1998, now abandoned.

(30) **Foreign Application Priority Data**

Jun. 9, 1997 (IL) ..... 121041

(51) **Int. Cl.****A61K 39/395** (2006.01)**C07P 16/00** (2006.01)**C12P 21/08** (2006.01)(52) **U.S. Cl.** ..... **424/141.1; 424/130.1; 424/133.1; 530/387.1; 530/388.1**(58) **Field of Classification Search** ..... **530/300, 530/350, 387.1, 387.2; 424/184.1**  
See application file for complete search history.(56) **References Cited****U.S. PATENT DOCUMENTS**5,068,177 A \* 11/1991 Carson et al. .... 424/131.1  
5,874,209 A 2/1999 Karin et al.**FOREIGN PATENT DOCUMENTS**EP 0438312 \* 7/1991  
WO WO 92/13970 8/1992  
WO WO 93/18792 9/1993  
WO WO 96/01126 1/1996  
WO WO 97/04092 2/1997  
WO WO 98/1885 5/1998**OTHER PUBLICATIONS**Jannot et al., BBRC 230:242-246, 1997.\*  
Erez-Alon et al., Cancer Res. 58:5447-5452, 1998.\*

Cruse et al (Illustrated dictionary of Immunology, CRC Press, 1995, p. 148.\*

Zusman et al. The Cancer Journal. 1997, 10:116-120.\*

Jannot et al. BBRC, 1997, 230:242-246.\*

Cohen, "Natural Id-Anti-Id Networks and the Immunological Homunculus", in *Theories of Immune Networks* (Atlan et al, ed.), Springer-Verlag, Heidelberg (1989) pp. 6-12.Cohen, "The cognitive paradigm and the immunological homunculus", *Immunol Today* 13(12):490-494 (1992).El-Deiry et al, "Definition of a consensus binding site for p53", *Nature Genet* 1(4):45-49 (1992).Foord et al, "A DNA binding domain is contained in the C-terminus of wild type p53 protein", *Nucleic Acids Res* 19(19):5191-5198 (1991).Gannon et al, "Activating mutations in p53 produce a common conformational effect. A monoclonal antibody specific for the mutant form", *EMBO J* 9(5):1595-1602 (1990).Harlow et al, "Monoclonal antibodies specific for simian virus 40 tumor antigens", *J Virol* 39:861-869 (1981).Hollstein et al, "p53 mutations in human cancers", *Science* 253:49-53 (1991).Houbiers et al, "In vitro induction of human cytotoxic T lymphocyte responses against peptides of mutant and wild-type p53", *Eur J Immunol* 23:2072-2077 (1993).Jannot et al, "Characterization of scFv-421, a Single-Chain Antibody Targeted to p53", *Biochem Biophys Res Comm* 230:242-246 (1997).Lee et al, "p53 and its 14Kda C-terminal domain recognize primary DNA damage in the form of insertion ~~deletion~~", *Cell*, 81:1013-1020 (1995).Lubin et al, "Analysis of p53 30 antibodies in patients with various cancers define B-cell epitopes of human p53: distribution on primary structure and exposure on protein surface", *Cancer Res* 53:5872-5876 (1993).

(Continued)

*Primary Examiner*—Gary Nickol*Assistant Examiner*—Sean E Aeder(74) *Attorney, Agent, or Firm*—Winston & Strawn LLP(57) **ABSTRACT**

The invention relates to the use of an immunogen selected from the group consisting of

- (i) an anti-p53 mAb;
- (ii) a fragment of an anti-p53 mAb;
- (iii) a peptide based on a CDR of the heavy or light chain of an anti-p53 mAb, which peptide is capable of eliciting antibodies to p53; and
- (iv) a DNA molecule coding for the variable (V) region of an anti-p53 mAb in a suitable gene delivery vehicle, for the preparation of a pharmaceutical composition useful for induction of anti-tumor immunity in mammals, for activating an enhanced immune response to a p53 molecule in mammals, and/or for induction of immune responses to mutated and wild-type forms of a p53 in mammals. The use of anti-p53 mAbs and novel peptides based on the CDR2 and CDR3 of the heavy chains and CDR3 of the light chains of different anti-p53 mAbs are disclosed.

**15 Claims, 5 Drawing Sheets**

-continued

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 20

What is claimed is:

1. A synthetic peptide capable of eliciting antibodies to p53, which peptide is 7 to 30 amino acids in length of a variable region of an anti-p53 mAb and contains a sequence of a CDR of the heavy chain or light chain of the anti-p53 mAb, and salts thereof, wherein the sequence of the CDR is selected from the polypeptide sequences of mAb 240, mAb 246 and mAb 421.

acid residues

2. A synthetic peptide according to claim 1, containing a sequence of the CDR2 or CDR3 of the heavy chain, or of the CDR3 of the light chain, of an anti-p53 mAb.

3. A synthetic peptide according to claim 1, wherein the peptide contains a sequence selected from the group of sequences consisting of Ic (SEQ ID NO:11), IIa (SEQ ID NO:12), and IVc (SEQ ID NO:20).

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4. A synthetic peptide according to claim 3, wherein the peptides are selected from the group consisting of peptides V–VII of the sequences:

Peptide V: Tyr-Tyr-Cys-Gln-His-Ile-Arg-Glu-Leu-Thr-Arg-Ser-Glu-Gly-Gly-Pro-Ser (SEQ ID NO:21),

Peptide VI: Gly-Val-Tyr-Tyr-Cys-Trp-Gln-Gly-Thr-His-Ser-Pro-Leu-Thr-Phe-Gly-Ala-Gly-Thr-Lys (SEQ ID NO:22),

Peptide VII: Gly-Asp-Ile-Asn-Pro-Asn-Asn-Gly-Tyr-Thr-Ile-Tyr-Asn-Gln-Lys-Val-Lys-Gly-Lys-Ala (SEQ ID NO:23), and salts thereof.

5. A synthetic peptide according to claim 1, wherein the peptide contains the sequence: Gln-His-Ile-Arg-Glu-Leu-Thr-Arg (SEQ ID NO:11) or Tyr-Tyr-Cys-Gln-His-Ile-Arg-Glu-Leu-Thr-Arg-Ser-Glu-Gly-Gly-Pro-Ser (SEQ ID NO:21).

6. The peptide of claim 1 in the form of an organic or inorganic salt thereof.

7. The peptide of claim 2, wherein the peptide is selected from the group consisting of:

(i) peptides, herein designated Ia–Ib, containing the CDR2 and CDR3, respectively, of the heavy chain (240VH), and peptide Ic containing the CDR3 of the light chain (240VL), of the anti-p53 mAb 240, of the sequences: (Ia) Glu-Ile-Asp-Pro-Ser-Asp-Ser-Tyr-Thr-Asn-Tyr-Asn-Gln-Phe-Lys-Asp (SEQ ID NO:9), (Ib)

Asn-

(IIa) Asp-Ile-Asn-Pro-Asn-Asn-Gly-Tyr-Thr- (SEQ ID NO:12), Ile-Tyr-Asn-Gln-Lys-Val-Lys-Gly

(IIb) Gly-Gly-Gly-Leu-Lys-Gly-Tyr-Pro-Phe- (SEQ ID NO:13), or Val-Tyr

(IIc) Gln-Gln-Arg-Ser-Ser-Phe-Pro-Phe-Thr (SEQ ID NO:14);

Leu-Leu-Arg-Tyr-Phe-Ala-Met-Asp-Tyr (SEQ ID NO:10), or (Ic) Gln-His-Ile-Arg-Glu-Leu-Thr-Arg (SEQ ID NO:11);

(ii) peptides, herein designated IIa–IIb, containing the CDR2 and CDR3, respectively, of the heavy chain

8. A pharmaceutical composition comprising the peptide of claim 1 and a pharmaceutically acceptable carrier.

9. The pharmaceutical composition of claim 8, wherein the peptide contains a sequence of the CDR2 or CDR3 of the heavy chain, or of the CDR3 of the light chain, of an anti-p53 mAb.

10. The pharmaceutical composition of claim 9, wherein the peptide contains the sequence: Gln-His-Ile-Arg-Glu-Leu-Thr-Arg (SEQ ID NO:11) or Tyr-Tyr-Cys-Gln-His-Ile-Arg-Glu-Leu-Thr-Arg-Ser-Glu-Gly-Gly-Pro-Ser (SEQ ID NO:21).

11. The pharmaceutical composition of claim 8, wherein the peptide is selected from the group consisting of:

(i) peptides, herein designated Ia–Ib, containing the CDR2 and CDR3, respectively, of the heavy chain (240VH), and peptide Ic containing the CDR3 of the light chain (240VL), of the anti-p53 mAb 240, of the sequences: (Ia) Glu-Ile-Asp-Pro-Ser-Asp-Ser-Tyr-Thr-Asn-Tyr-Asn-Gln-Asn-Phe-Lys-Asp (SEQ ID NO:9), (Ib) Leu-Leu-Arg-Tyr-Phe-Ala-Met-Asp-Tyr (SEQ ID NO:10), or (Ic) Gln-His-Ile-Arg-Glu-Leu-Thr-Arg (SEQ ID NO:11);

(ii) peptides, herein designated IIa–IIb, containing the CDR2 and CDR3, respectively, of the heavy chain (246VH), and peptide 11c containing the CDR3 of the light chain (246VL), of the anti-p53 mAb 246, of the sequences:

(iii) peptides, herein designated IVa–IVb, containing the CDR2 and CDR3, respectively, of the heavy chain (421VH), and peptide IVc containing the CDR3 of the light chain (421VL), of the anti-p53 mAb 421, of the sequences:

(IVa) Trp-Ile-Asp-Pro-Glu-Asn-Gly-Asp-Thr- (SEQ ID NO:18), Glu-Tyr-Ala-Pro-Lys-Phe-Gln-Gly

(IVb) Tyr-Gly-Asp-Ala-Leu-Asp-Tyr (SEQ ID NO:19), or

(IVc) Trp-Gln-Gly-Thr-His-Ser-Pro-Leu-Thr (SEQ ID NO:20);

(246VH), and peptide 11c containing the CDR3 of the light chain (246VL), of the anti-p53 mAb 246, of the sequences: (IIa) Asp-Ile-Asn-Pro-Asn-Asn-Gly-Tyr-Thr-Ile-Tyr-Asn-Gln-Lys-Val-Lys-Gly (SEQ ID NO:12), (IIb) Gly-Gly-Gly-Leu-Lys-Gly-Tyr-Pro-Phe-Val-Tyr (SEQ ID NO:13), or (IIc) Gln-Gln-Arg-Ser-Ser-Phe-Pro-Phe-Thr (SEQ ID NO:14);

(iii) peptides, herein designated IVa–IVb, containing the CDR2 and CDR3, respectively, of the heavy chain (421VH), and peptide IVc containing the CDR3 of the light chain (421VL), of the anti-p53 mAb 421, of the sequences: (IVa) Trp-Ile-Asp-Pro-Glu-Asn-Gly-Asp-Thr-Glu-Tyr-Ala-Pro-Lys-Phe-Gln-Gly (SEQ ID NO:18), (IVb) Tyr-Gly-Asp-Ala-Leu-Asp-Tyr (SEQ ID NO:19), or (IVc) Trp-Gln-Gly-Thr-His-Ser-Pro-Leu-Thr (SEQ ID NO:20); and salts thereof.

and salts thereof.

12. The pharmaceutical composition of claim 8, wherein the peptide contains a sequence selected from the group of sequences consisting of Ic (SEQ ID NO:11), IIa (SEQ ID NO:12), and IVc (SEQ ID NO:20).

13. The pharmaceutical composition of claim 12, wherein the peptides are selected from the group consisting of peptides V–VII of the sequences:

Peptide V: Tyr-Tyr-Cys-Gln-His-Ile-Arg-Glu-Leu-Thr-Arg-Ser-Glu-Gly-Gly-Pro-Ser (SEQ ID NO:21),

Peptide VI: Gly-Val-Tyr-Tyr-Cys-Trp-Gln-Gly-Thr-His-Ser-Pro-Leu-Thr-Phe-Gly-Ala-Gly-Thr-Lys (SEQ ID NO:22),

Peptide VII: Gly-Asp-Ile-Asn-Pro-Asn-Asn-Gly-Tyr-Thr-Ile-Tyr-Asn-Gln-Lys-Val-Lys-Gly-Lys-Ala (SEQ ID NO:23), and salts thereof.

Phe

CDR3